## REMARKS

In the final Office Action claims 1, 2, 4-26, 28-50, 53, and 54 were pending, claims 7, 15-24, 31, 39-48, 53 and 54 are withdrawn from consideration, and claims 1, 2, 5, 6, 8-14, 25-30, 32-38, 49 and 50 stand rejected.

Previously withdrawn claims 7, 15-24, 31, 39-48, 53 and 54 are herewith canceled without prejudice or disclaimer as to the subject matter thereof.

Following entry of the present Amendment After Final claims 1, 2, 5, 6, 8-14, 25-30, 32-38, 49 and 50 are pending examination on the merits.

Applicant herewith tenders amendments to just the independent claims intended to place the application in condition for allowance and were not earlier submitted because the procedural posture of the application (e.g., the then-present grounds of rejection) did not admit of same. Applicant respectfully suggests that the amendments tendered herewith do not raise additional issues requiring additional search of the applicable prior art and should place the pending claims in condition for allowance.

Applicant respectfully requests entry of and favorable consideration of the amendments and remarks contained herein so that the pending claims may pass to timely issuance as U.S. Letters Patent.

### I. Claim Rejections Under 35 U.S.C. §103

All pending claims stand rejected as obvious over various combinations of references. However, Applicant respectfully suggests that, as only a single inventor conceived and reduced to practice the subject matter of the instant application, the Examiner erred by including the form paragraph regarding 35 U.S.C. §103(c), 102(f) and 102(g) regarding multiple inventors.

In addition, it appears as though the Examiner perhaps incorrectly recited the publication number for the reference to an inventor named German. Applicant suggests that the correct number is: as 2003/0078226 A1 (and not 2003/0078266 A1 as recited in the final Office Action).

Applicant herewith amends the pending independent claims; namely, claim 1, 25 and 49 in particular to distinguish the claimed subject matter from the primary reference applied by the Examiner, the Brown reference. Inasmuch as said amended independent claims in fact distinguish Brown, Applicant suggests that all claims pending therefrom are also patentably distinct from Brown and as such, should be allowed.

The specific claim rejections are set forth below and each is addressed in turn hereinbelow.

**A.** Claims 25, 26, 28, 29, 32, 33 and 49 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Pat. No. 6,219,577 to Brown et al. (Brown) in view of U.S. Pat. No. 6,273,875 to Siman et al. (Siman).

**B.** Claims 1, 2, 4, 5, 8-10, 25-29, 32, 33, 35, 49, and 50 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brown in view of Siman and Gunzburg (WO 96/28563).

**C.** Claims 1, 4-6, 25 and 28-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brown in view of Siman and Gunzburg in further view of U.S. Pat. No. 6,451,044 to Naghavi (Naghavi) or U.S. Pat. No. 6,206,914 to Soykan (Soykan).

**D.** Claims 1, 4, 5, 8-14, 25, 26, 28, 32-38, 49, and 50 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brown in view of published U.S. patent application published as 2003/0078226 A1 to Siman and German (German).

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**A.** Claims 25, 26, 28, 29, 32, 33 and 49 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Pat. No. 6,219,577 to Brown et al. (Brown) in view of U.S. Pat. No. 6,273,875 to Siman et al. (Siman).

According to the Examiner, Brown discloses the claimed invention except for claim limitations recited in the pending claims. For example, with respect to claims 25, 26, 28, 29, 32, 33 and 49 Brown purportedly includes all claim limitations recited except for a polymer film applied to the exterior surface of the implantable medical device (IMD) housing. Applicant herewith directly amends independent claim 25 and claims 26, 28, 29, 32, 33 depending therefrom so that said claims are rendered patentably distinct from Brown. Likewise, Applicant herewith directly amends independent claim 49 to render it patentably distinct from Brown as well. In formulating the rejection, the Examiner indicates that "it would have been obvious" and "one of ordinary skill in the art would have been motivated" without reciting any specific passage from either Brown or Siman in support of the proposed combination of the art. Thus, Applicant strongly suggests that the Examiner has failed to meet his burden to set forth a *prima facie* obviousness rejection with respect to this ground of rejection, A (as well as grounds B through D).

In connection with combining references to support an assertion of obviousness, it is well established that the Examiner bears the burden of establishing a prima facie case of obviousness. In re Oetiker, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). In doing so, the Examiner must determine whether the prior art provides a "teaching or suggestion to one of ordinary skill in the art to make the changes that would produce" the claimed invention. In re Chu, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995). A prima facie case of obviousness is established only when this burden is met. The burden is still on the Examiner even when the Examiner relies upon a single reference. "Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." In re Kotzab, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000).

In the case of In re Lee, 61 USPQ2d 1430 (Fed. Cir. 2002), the Federal Circuit stated: "This factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority." Id. at 1434. Determination of patentability must be based on evidence, id. at 1434, and the Examiner provided none: no references pertaining to aggregation or averaging were cited, no official notice was taken, no evidence of any kind was presented. The Examiner's failure to present an

evidentiary basis for the decision is clearly a legal error. Id. Assertions such as "common knowledge and common sense," even if assumed to derive from the Examiner's expertise, are not evidence, and conclusory statements do not fulfill the Examiner's obligation to make an evidentiary record. Id. at 1434-35; In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

If indeed the elements were known in the art, then the Examiner ought to present evidence to support that conclusion. In re Lee, 61 USPQ2d at 1435 ("[W]hen they rely on what they assert to be general knowledge to negate patentability, that knowledge must be articulated and placed on the record."). The failure to do so renders the Examiner's rejection arbitrary, capricious and unreasonable. See id. at 1434. The Examiner may not arbitrarily, capriciously and unreasonably deny a claim by a mere declaration of obviousness without a supporting evidentiary record.

The Examiner presented no evidence of any suggestion or motivation to modify the Wilson techniques to arrive at the claimed invention. Nor has the Examiner presented any evidence that the recited elements are known in the art. The record consists exclusively of conclusory statements by the Examiner, which are not evidence and which cannot support rejections under 35 U.S.C. § 103. For at least the foregoing reasons, the Examiner has failed to establish a prima facie case for non-patentability of Applicant's claims under 35 U.S.C. § 103(a). Withdrawal of all grounds of rejection "A"-"D" is hereby earnestly and respectfully requested.

Regardless, in addition to the foregoing, Applicant has elected to amend the claims in particular to render said claims patentably distinct over the primary reference employed by the Examiner, Brown.

To that end, the following underlined text has been added to the end of independent claim 1: "... a polynucleotide associated with at least a portion of the polymer, whereby said polynucleotide encodes for an antimicrobial peptide, thus providing for an antimicrobial effect after said polynucleotide is released from said polymer film and said polynucleotide is expressed in and the encoded antimicrobial peptide is delivered by the cells and tissues surrounding said medical device."

Similarly, the following underlined text has been added to the end of independent claim 25: "... from the medical device upon being implanted in a patient, whereby said polynucleotide encodes for an antimicrobial peptide, thus providing an antimicrobial effect after said polynucleotide is expressed in and the encoded antimicrobial peptide is delivered by the cells and tissues surrounding said medical device."

Likewise, the following underlined text has been added to the end of independent claim 49: "... contacting the polymer with the polynucleotide, whereby said polynucleotide encodes for an antimicrobial peptide, thus providing for an antimicrobial effect after said polynucleotide is released from said polymer film and said polynucleotide is expressed in and the encoded antimicrobial peptide is delivered by the cells and tissues surrounding said medical device."

Overall Applicant suggests that the foregoing changes to the independent claim better discriminate the pending claim from Brown. As the primary prior art reference relied upon as the basis for all claim rejections in the final Office Action, once Brown is sufficiently distinguished all pending claims should be deemed allowable. Hitherto, the Examiner has not accepted the argument that the presently claimed invention is directed to chronically implanted medical devices and not to temporarily inserted medical devices (the latter being the only subject matter addressed by Brown). In support of this distinguishing feature of Brown versus the present invention, Brown discloses, at col. 3, lines 61-63, the following: "The present invention is particularly applicable to the local delivery of drugs during interventional cardiology procedures such as angioplasty, stent implantation etc." Further, in Brown at col. 4, lines 9-11: "...the catheter devices are similar in operation to current angioplasty catheter devices...". And Brown at col. 4, lines 31-32: "... to provide devices which can be used in blood vessels ...". Particularly these passages provide evidence for those skilled in the art that the medical devices that fall within the scope of Brown's patent have a temporary mode of action and, unlike the present invention, are not intended to be chronically implanted.

Moreover, Brown addresses only medical devices that are "...devices for electrically enhancing the local delivery of treatment agents into the wall tissues or cells

of the living body. These devices are designed to target certain tissue and cell locations, while minimizing any effects on non-targeted tissues and cells." (col. 3, lines 32-37).

In contrast to Brown's description of medical devices, the medical devices of the present invention are devices that do not have delivery of therapeutic agents as their primary mode of action. The anti-infection technology as disclosed in the present patent application is protective rather than therapeutic. Above and beyond the foregoing, the polynucleotide released in itself has no therapeutic action; it is the peptides that it encodes for, that are released by cells surrounding the medical device after the polynucleotide has come to expression in those same cells that have the therapeutic action.

Further, Brown's medical devices are directed to application in tubular tissues, see col. 4, lines 21-23: "... to provide for devices for the local delivery of treatment agents into the wall tissues or cells of the living body" (emphasis added); and at col. 8, lines 50-52: "Although the present inventions may have wider applications in locally delivering drugs to many different tubular tissues of the body...". These passages from Brown provide yet another limitation that is not relevant to the medical devices that fall within the scope of the present patent application.

Indeed, Brown teaches about the use of a polymer matrix for incorporation and subsequent delivery of pharmaceuticals (col. 15, all lines). However, the Examiner fails to see the (subtle) difference in the function of the polymer matrix when comparing the Brown patent and the instant invention. Brown discloses (at col. 15, lines 44-48): "[p]referable matrices would be tailored according to the molecular characteristics of the agent to restrict its loss by free diffusion outwards but allow full iontophoretic migration outwards when a potential is applied across the polymer and the adjacent tissue." The crux of this statement lies in the phrase "... to restrict its loss by free diffusion outwards ...". This phrase shows that in the context of Brown the medical device associated polymer coating is considered merely a drug container. According to Brown, delivery of the therapeutic is only triggered "... when a potential is applied across the polymer ...".

This is in stark contrast to the functional role of the polymer matrix according to the present invention whereby upon exposure to body fluids the polynucleotide

encoding for the antimicrobial peptide will be eluted by diffusion, *and whereby enhancement of a further exogenous trigger is not necessary.* Control of elution rate is obtained by control of polymer porosity, control of polynucleotide – polymer compatibility, control of polynucleotide-to-polymer ratio etc.

With respect to the other references combined with Brown, Applicant offers the following. For example, while Applicant maintains that the proposed combination of Brown with any the other references does not *per se* rise to the level of a *prima facie* rejection, and that the foregoing remarks regarding Brown should be dispositive of the rejections based thereon, some additional concerns involve the secondary and tertiary references applied by the Examiner.

**B.** Claims 1, 2, 4, 5, 8-10, 25-29, 32, 33, 35, 49, and 50 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brown in view of Siman and Gunzburg (WO 96/28563).

While Siman (US 6,273,875 B1) admittedly discloses providing a medical device with a polymeric coating to obtain antimicrobial and antithrombogenic properties, the technology disclosed can in no way be compared to the teachings of the present invention. The combination of Brown and Siman patents does not seem appropriate given the fact that Siman teaches (at col. 4, lines 40-41): "...the antibacterial effect will begin as soon as the medical device is implanted because of ...". This is in *stark contrast* with the polymer matrix system as described as being preferred by Brown (above). Brown's definition of medical devices is not in sync with the definition of interest for the medical devices with respect to the instant invention, and thus the combination of Brown and Siman cannot be considered appropriate for the purpose of rejecting the pending claims. In fact, contrary to Brown, Siman discloses in an Example 3 (col. 8, lines 40-43) the notion that extant "...coatings for medical devices including pacers, defibrillators, valves, ....".

However, the medical devices mentioned by Siman would be relevant with respect to the devices of interest with respect to the present invention, but (i) on its own Siman's patented technology as disclosed cannot be compared to that of the present

invention (see also next paragraph); (ii) the combination with Brown does not appear justified, as this list of devices in the Siman patent is not in sync with those that befit the typical devices as taught by Brown.

Further objections against the Siman reference relate to the following fact: the polymer coating of the instant invention has no intrinsic antimicrobial properties, much *unlike* the coating disclosed by Siman. Rather, local antimicrobial effects are achieved because surrounding cells and/or tissues deliver the antimicrobial agents (after having been transfected with the eluted polynucleotide) and not because these are directly delivered from the coating. The suggested amendments to the independent claims herein are intended to elucidate this point.

Further, the Gunzburg patent only holds when taken with Brown and Siman as suggested by the Examiner. Hereinabove Applicant remarks that Brown and Siman are neither independently nor when combined relevant to the scope of the presently claimed subject matter. The fact that Brown alone can be readily distinguished from the present invention and that the combination of Brown and Siman is inapposite further damages the additional inclusion of Gunzburg (as potentially non-analogous art). This fact also undermines the relevance of all combinations using Brown (and/or Siman). If anything, the Gunzburg patent can be considered relevant in support of the conceptual idea disclosed in the specification of the present application. Nowhere in the Gunzburg application is a reference to medical device associated infections.

**C.** Claims 1, 4-6, 25 and 28-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brown in view of Siman and Gunzburg in further view of U.S. Pat. No. 6,451,044 to Naghavi (Naghavi) or U.S. Pat. No. 6,206,914 to Soykan (Soykan).

With respect to the rejections based on Brown taken with Siman and Gunzburg and in view of either Naghavi or Soykan: Applicant suggests that if the Examiner were able to combine each and every patent without meeting the burden of a *per se* requirement for obviousness, most everything appears obvious. Again, neither Naghavi nor Soykan holds any credibility against the presently claimed invention when taken

singly. Again, Applicant suggests that Brown has been sufficiently distinguished and thus cannot be used as a primary reference to support a *prima facie* obviousness rejection and thus the present ground of rejection is flawed and should be withdrawn.

First of all, as mentioned hereinabove, the Examiner seems not to have transcribed the correct reference for the patent application by German, Applicant respectfully suggest that the correct publication number is: US 2003/0078226 A1.

While German discloses - in general terms - about gene therapy for the treatment of infections, it does not do so in any relation to chronically-implanted medical device associated infections. German's application appears to be particularly aimed at genetic transformation of secretory gland cells for achieving a systemic effect. (See par. 002: "This invention relates generally to delivery of a substance to the bloodstream of a subject, in particular to bloodstream-directed delivery of a polypeptide.") This is in very stark contrast to the claimed subject matter of the present invention, which is directed to achieving local antimicrobial effects as to protect an implanted medical device and its surrounding cells and tissues from pathogenic microorganisms. The combination of Brown and Siman and German is therefore not relevant, further extending the remarks provided hereinabove.

**D.** Claims 1, 4, 5, 8-14, 25, 26, 28, 32-38, 49, and 50 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brown in view of published U.S. patent application published as 2003/0078226 A1 to Siman and German (German).

The final argument of the Examiner concerns Brown taken with German regarding condensed polynucleotides, targeting ligands, and liposome carriers. The Examiner's position can be negated when considering the foregoing remarks that Brown is not relevant to the present invention and that German teaches the application of said techniques for systemic application (*see* para. 002: "... delivery of a substance to the bloodstream ...").

## II. Conclusion

Applicant submits that all pending claims are in condition for allowance and requests that a notice of allowance should be issued in due course. The Examiner is invited to contact the undersigned to discuss any questions regarding the present application.

Respectfully submitted,

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